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Expeditious Copper-Catalyzed Conjugate 1,4-Addition of Bromo[2-(1,3-dioxolan-2-yl)ethyl]magnesium to α,β-Cycloalkenones and Subsequent Transformations

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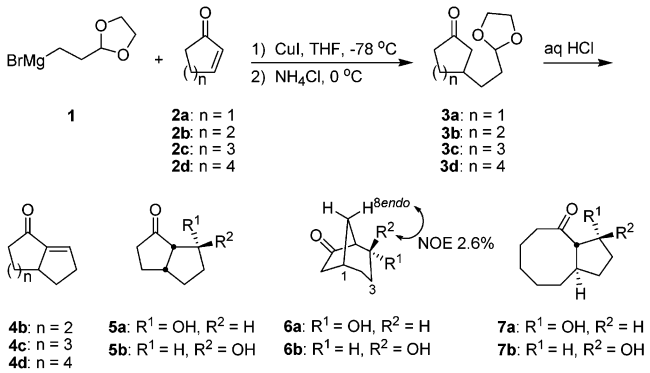
Abstract: Expeditious CuI-catalyzed conjugate 1,4-addition of bromo[2-(1,3-dioxolan-2-yl)ethyl]magnesium to the five-, six-, seven-, and eight-membered α,β-cycloalkenones is described. The reaction times are decreased dramatically compared to CuBr−$(CH_3)_2S$ catalysis. The resulting keto-acetals were subsequently cyclized to bicyclic β-hydroxy ketones and α,β-enones, followed by further transformations.

Conjugate 1,4-addition of acetal-containing Grignard reagents to α,β-unsaturated ketones followed by annulation[1−5] comprises an important class of reactions because the resulting ring systems intervene in the synthesis of many natural products and useful compounds as, for example, in the total synthesis of hymenolin,[6a] parthenin,[6a,b] ceroplastin sesterterpenes,[6c] pentacyclic triterpenes,[6d] axanes,[6e] 7,8-epoxy-2-basmen-6-one,[6f] ptilocaulin,[6g,h] retigeranic acid A,[6i] senoxydene,[6j] dehydrocostus lactone,[6k] estafiatin,[6k] silphiperfol-6-ene,[6l] oxosilphiperfol-6-ene,[6l] silphinene,[6m] isocomene,[6n] modhephene,[6o] and others.[5,6p,q,r]

SCHEME 1. CuI-Catalyzed 1,4-Addition of 1 to 2 and Subsequent Cyclization



Conjugate 1,4-addition of bromo[2-(1,3-dioxolan-2-yl)-ethyl]magnesium (**1**) to the α,β-cycloalkenones **2a**−**c** under CuBr−$(CH_3)_2S$ catalysis has been previously reported by Helquist and associates.[3] The experimental procedures are, however, unnecessarily time-consuming, with the addition of **1** to **2** requiring 4 h followed by stirring at −78 °C for an additional 15 h.

We report herein the conjugate 1,4-addition of Grignard reagent **1** to the α,β-cycloalkenones **2** under CuI catalysis. The reaction of **1** with **2d** is unprecedented. The enones **2** were converted smoothly into the corresponding ketoacetals **3** with the exception of **2a**, "a notoriously difficult case for conjugate additions",[3] which afforded a moderate yield of ketoacetal **3a** (Scheme 1). The use of $CeCl_3$[6d] in place of CuI did not improve the yield. Our results are in part comparable to those of Helquist; however, *the overall reaction times are decreased dramatically*.

Prior to the use of CuI, we employed the conditions reported by Helquist,[3] with the modification that the addition of the enone to the reaction mixture took place within 5 min instead of 4 h. The yield in ketoacetal was satisfactory with enone **2b**, but not with **2a**,**c**,**d**. We have also carried out addition of **1** to enone **2b** at −78 °C in the absence of CuI, according to conditions reported by Sworin.[2] The yield in ketoacetal **3b** was less satisfactory, and the reaction mixture was complicated by the presence of the 1,2-addition product and by heavier products resulting from consecutive 1,4- and 1,2-additions.

The ketoacetals **3** were isolated and hydrolyzed with aq HCl. Thus, **3b**,**c** afforded the bicyclic enones **4b**,**c**, as reported by Helquist.[3] The ketoacetal **3d** furnished a mixture of the enone **4d** and the *trans*-diastereomeric β-hydroxy ketones **7a**,**b**. Apparently, the *trans* isomers are thermodynamically more stable relative to the *cis*. Interestingly, **3a** gave, in addition to **5a**, the three diastereomeric β-hydroxy ketones **5b** and **6a**,**b**, not previously observed. Yields are presented in Table 1.

Structural assignments were based on NMR experiments (including NOE, paramagnetic shifts reagents, and COSY), on conversion of the reaction products to known compounds, and on the preparation of authentic samples. Thus, an NOE was observed with **6a** but not with **6b**. With the use of $Eu(fod)_3$,[7] we have accomplished resolu-

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TABLE 1. Ketoacetals and Annulation Products

enone	ketoacetal (yield, %)[a]	annulation product (yield, %)[a]
2b[b]	**3b** (92)	**4b** (93)
2c[b]	**3c** (88)	**4c** (90)
2d[b]	**3d** (89)	**4d** (15) + **7a** (38) + **7b** (31)
2a[c]	**3a** (43)	**5a** (53) + **5b** (9) + **6a** (20) + **6b** (3)

[a] Isolated. [b] Two equiv of Grignard reagent **1** were used. [c] Four equiv of **1** were used.

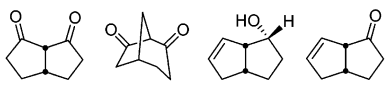
TABLE 2. NMR Pseudo-Contact Shifts in 6a and 6b Induced by Eu(fod)$_3$

	$\Delta\delta$ ^{1}H[a]			$\Delta\delta$ ^{13}C[a]	
H	**6a**	**6b**	C	**6a**	**6b**
1	0.22	0.35	1	0.41	0.58
2*exo*	0.23	0.62	2	0.23	0.65
2*endo*	0.23	0.38			
3*exo*	0.53	0.76	3	0.32	0.63
3*endo*	0.84	0.55			
4	0.73	1.48	4	2.46	2.65
5	0.81	1.08	5	0.84	0.70
6			6	1.69	1.53
7*exo*	0.42	0.56	7	0.32	0.60
7*endo*	0.49	0.56			
8*exo*	0.25	0.48	8	0.39	0.80
8*endo*	0.22	0.82			

[a] Chemical shift difference estimated at [Eu(fod)$_3$]/[compd] = 0.070 for **6a** and **6b**.

tion of all the protons in **6a** and **6b**. A total of three additions of Eu(fod)$_3$ were performed (see Tables S1 and S2, Supporting Information), and after each addition, (H,H)- and (H,C)-COSY were obtained to identify proton and carbon atoms. Plots were constructed next (the relationships were linear, or nearly linear) in order to compare the lanthanide induced shifts (LIS) in **6a** and **6b** at the same [Eu(fod)$_3$]/[compound] ratio. The results (Table 2) confirm the stereochemistry assigned to **6a** and **6b**. Noticeable are the H^{2exo}, H^{3exo}, H^{8endo}, and C^8 LIS which are greater in **6b** (*exo*-OH), compared to the corresponding LIS in **6a** (*endo*-OH). The reverse is observed with the LIS of H^{3endo}.

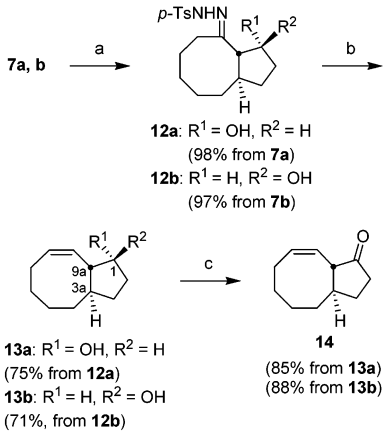
The *β*-hydroxy ketones **7a**,**b** were partially converted to the same enone **4d** with 20% aq H_2SO_4, the rate of elimination of **7a** being greater than that of **7b**. Oxidation of **5a**,**b** and **6a**,**b** with PCC furnished the known 1,3-diones **8**[8] and **9**,[9] respectively. The *β*-hydroxy ketone **5a** was converted to the olefinic alcohol **10** via its *p*-tosylhydrazone derivative followed by reaction with methyllithium and found to be identical with an authentic sample.[10] Oxidation of alcohol **10** with CrO_3-pyridine complex[11] gave the known[10] enone **11**.



8 **9** **10** **11**

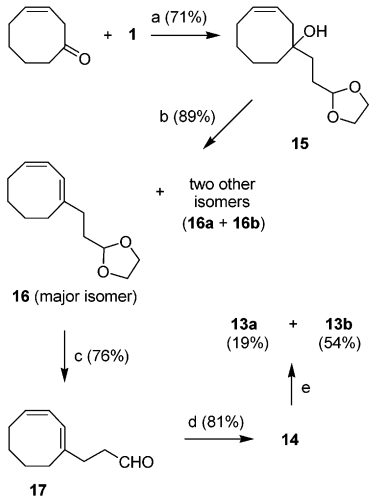
The *β*-hydroxy ketones **7a**,**b** were converted to the corresponding *p*-tosylhydrazones **12a**,**b** as depicted in Scheme 2. Elimination of these with butyllithium (BuLi) to the alkene alcohols **13a**,**b** followed by Swern[12] oxidation afforded the same enone **14**. An authentic sample of **14** was prepared as shown in Scheme 3. Thus, conjugate 1,2-addition of the Grignard reagent **1** to 3-cycloocten-1-one[10] furnished cyclooctanol **15**, which was eliminated with $POCl_3$ affording diene **16**, as the major product, and the other two possible isomeric dienes **16a** and **16b** (see the Supporting Information). Hydrolysis of **16** was carried out with AcOH−H_2O (1:1) and gave dienal **17**, which was cyclized with $MeAlCl_2$ to enone **14** according to a procedure described in the literature.[13] Reduction of the latter with DIBAL-H furnished the diastereomeric alcohols **13a**,**b**. This is an alternative route for preparing these two alcohols.

SCHEME 2. Conversion of 7a and 7b to 14[a]



[a] Reagents and conditions: (a) *p*-TsNHNH$_2$, CH_3OH, 25 °C, 15−20 h; (b) BuLi, TMEDA, THF, 25 °C, 17−21 h; (c) Swern oxidation.

SCHEME 3. Preparation of Authentic 14[a]



[a] Reagents and conditions: (a) THF, 25 °C, 1 h; (b) $POCl_3$, pyridine, 25 °C, 21 h; (c) AcOH−H_2O (1:1), 25 °C, 77 h; (d) $MeAlCl_2$, CH_2Cl_2, 5−25 °C, 21 h; (e) DIBAL-H.

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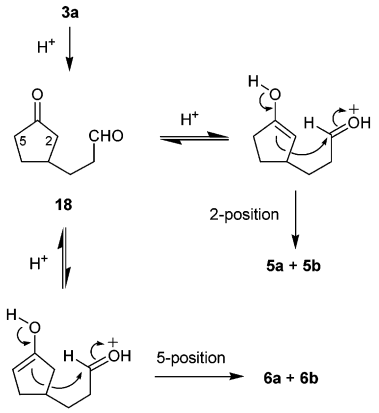
SCHEME 4. Aldol Condensation of 3a



NMR experiments with **13a**, **13b**, and Eu(fod)$_3$ followed by analysis of the data as described above, albeit less elaborate (see Table S3, Supporting Information), indicated that the proton at the 3a-position in **13a** (*cis* to the OH) was shifting downfield more rapidly than the corresponding in **13b** (*trans* to the OH), estimated at [Eu(fod)$_3$]/[compound] = 0.070 ($\Delta\delta^{3a}$ = 1.32 for **13a** vs 0.30 for **13b**). The reverse was observed with the proton at the 9a-position ($\Delta\delta^{9a}$ = 0.70 for **13a** vs 0.84 for **13b**), even though the shift difference in this case was less pronounced.

Mechanistically, it is apparent that the alcohols **5a**,**b** are obtained as a result of intramolecular aldol condensation at the 2-position, whereas **6a**,**b** come from condensation at the 5-position of the keto aldehyde **18** via the two different enol intermediates, as shown in Scheme 4. Analogous examples are cited in the literature.[14] This was not observed in any other case studied.

In conclusion, we have shortened dramatically the reaction times for the addition of the Grignard reagent **1** to the cycloalkenones **2** by the use of CuI instead of CuBr−$(CH_3)_2S$ catalysis,[3] also avoiding the unpleasant odor of $(CH_3)_2S$. In addition, we have identified three more isomeric annulation products in the case of enone **2a**, and placed the eight-membered enone **2d** under the aegis of this important class of reactions.

Experimental Section

Column chromatography was performed with columns containing silica gel (70−270 mesh). Columns used: A (85 × 2.5 cm, filled with 180 g), B (26 × 2.0 cm, 32 g), C (46 × 1.6 cm, 33 g), D (60 × 2.0 cm, 75 g), E (70 × 2.0 cm, 82 g). The columns were eluted with petroleum ether (bp 65−69 °C)/ethyl acetate *x*:*y* (v/v). The cycloalkenones **2** were prepared as described in the literature.[15]

General Procedure for Conjugate Addition and Subsequent Annulation, by Example. 1,2,5,6,7,7a-Hexahydro-4*H*-inden-4-one (4b). To ground Mg turnings[2,3] (3.09 g, 127 mmol) in THF (25 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (11.37 g, 62.8 mmol) in THF (25 mL) at 22−24 °C[2] over a period of 15 min. After being stirred for 30 min, the mixture was cooled to −30 °C, CuI (1.19 g, 6.2 mmol) was added all at once, the mixture was stirred for 15 min and cooled to −78 °C, a solution of **2b** (3.00 g, 31.2 mmol) in THF (25 mL) was added within 5 min, and the mixture was warmed to 0 °C within 1 h and quenched with 30% NH_4Cl (adjusted to pH 8).[3] The mixture was extracted with CH_2Cl_2, dried, and concentrated. Column chromatography (column A, *x*/*y*: 10/1, then 5/1) afforded the Wurtz-type coupling product (250 mg) and the ketoacetal **3b**[3] (5.68 g, 92%, colorless oil). Hydrolysis of **3b** (5.68 g, 28.6 mmol) was accomplished by refluxing with 2.5% aq HCl (50 mL) in THF (50 mL) for 1 h. Neutralization with 5% aq $NaHCO_3$, extraction with CH_2Cl_2, drying, concentration, and column chromatography (column A, *x*/*y*: 10/1) furnished the enone **4b**[3] (3.62 g, 93%, colorless oil).

1,2,5,6,7,8,9,9a-Octahydro-4*H*-cyclopenta[*a*]cycloocten-4-one (4d), *rac*-(3*R*,3a*S*,9a*R*)-3-Hydroxydecahydro-4*H*-cyclopenta[*a*]cycloocten-4-one (7a), and *rac*-(3*S*,3a*S*,9a*R*)-3-Hydroxydecahydro-4*H*-cyclopenta[*a*]cycloocten-4-one (7b). Reagents: Mg (5.90 g, 243 mmol), 2-(2-bromoethyl)-1,3-dioxolane (14.6 g, 80.7 mmol), CuI (1.55 g, 8.1 mmol), **2d** (5.00 g, 40.3 mmol). Column chromatography (column A, *x*/*y*: 10/1, then 5/1) afforded 3-[2-(1,3-dioxolan-2-yl)ethyl]cyclooctanone (**3d**) (8.13 g, 89%, pale-yellow oil). Hydrolysis of **3d** (8.13 g, 35.9 mmol) followed by column chromatography (column A, *x*/*y*: 10/1, then 5/1) furnished the enone **4d** (0.879 g, 15%, first fraction, colorless oil), and the keto alcohols **7a** (2.49 g, 38%, second fraction, pale-yellow oil) and **7b** (2.02 g, 31%, third fraction, white crystalline solid). In a different hydrolysis experiment, **4d** (31.54 g, 139.4 mmol) was heated at reflux with 20% aq H_2SO_4 (150 mL) in THF (200 mL) for 2 h. Workup and column chromatography as above gave **4d** (9.12 g, 40%), **7a** (3.17 g, 12%), and **7b** (7.76 g, 31%). Compound **3d**: IR ν 1734, 1696, 1142, 1088, 1039 cm^{-1}; ^{1}H NMR δ 1.13−1.28 (m, 1H), 1.31−1.52 (m, 4H), 1.59−1.78 (m, 4H), 1.79−2.08 (m, 4H), 2.28−2.52 (m, 4H), 3.82−4.02 (m, 4H), 4.85 (t, J = 4.7 Hz, 1H); ^{13}C NMR δ 23.7, 24.8, 27.6, 31.3, 31.5, 33.3, 37.7, 42.9, 47.2, 64.88, 64.90, 104.5, 217.0; MS (EI) *m*/*z* (% relative abundance) 226 (M$^+$, 60), 182 (21), 152 (10), 135 (100), 99 (57), 87 (31), 73 (89). Anal. Calcd for $C_{13}H_{22}O_3$ (MW 226.312): C, 68.99; H, 9.80. Found: C, 69.10; H, 9.71. Compound **4d**: UV λ_{max} (ϵ) 257 (2550) nm; IR ν 1702, 1600, 1454, 1324 cm^{-1}; ^{1}H NMR δ 1.17−2.07 (m, 9H), 2.08−2.67 (m, 4H), 2.83 (ddd, J = 11.0, 8.8, 8.8 Hz, 1H), 3.10 (m, 1H), 6.71 (m, 1H); ^{13}C NMR δ 25.88, 25.93, 28.6, 31.0, 33.5, 37.0, 39.7, 44.1, 141.5, 148.6, 203.6; MS (EI) *m*/*z* (% relative abundance) 165 (M$^+$ + 1, 100) 164 (M$^+$, 47), 146 (5), 136 (9), 121 (23), 108 (14), 107 (14), 93 (45), 80 (32), 79 (19). Anal. Calcd for $C_{11}H_{16}O$ (MW 164.244): C, 80.44; H, 9.82. Found: C, 80.19; H, 9.58. Compound **7a**: IR ν 3620, 3455, 1670, 1172, 1073, 1042, 983 cm^{-1}; ^{1}H NMR δ 1.02−1.38 (m, 3H), 1.44−2.17 (m, 9H), 2.37−2.62 (m, 4H), 4.05 (br s, 1H, OH), 4.41 (t, J = 4.0 Hz, 1H); ^{13}C NMR δ 22.9, 24.9, 28.2, 30.9, 31.4, 33.6, 44.3, 46.4, 58.0, 75.8, 221.6; MS (EI) *m*/*z* (% relative abundance) 183 (M$^+$ + 1, 93), 182 (M$^+$, 4), 165 (55), 164 (11), 154 (31), 153 (9), 147 (10), 138 (100), 125 (25), 111 (14). Anal. Calcd for $C_{11}H_{18}O_2$ (MW 182.259): C, 72.49; H, 9.95. Found: C, 72.49; H, 10.07. Compound **7b**: mp (white needles from ethyl ether) 64−65 °C; IR ν 3615, 3450, 1688, 1082 cm^{-1}; ^{1}H NMR δ 1.05−1.19 (m, 1H), 1.19−1.34 (m, 1H), 1.44−1.75 (m, 5H), 1.75−1.97 (m, 4H), 2.03−2.20 (m, 2H), 2.43 (m, 2H), 2.75 (dd, J = 11.1, 8.4 Hz, 1H), 2.99 (br s, 1H, OH), 4.51 (ddd, J = 8.4, 8.4, 6.5 Hz, 1H); ^{13}C NMR δ 23.3, 24.8, 28.0, 30.8, 32.0, 32.2, 43.4, 47.1, 63.9, 75.6, 217.7; MS (EI) *m*/*z* (% relative abundance) 183 (M$^+$ + 1, 41), 182 (M$^+$, 3), 165 (51), 164 (100), 149 (13), 138 (18), 136 (33), 125 (24), 122 (24), 121 (29), 111 (19). Anal. Calcd for $C_{11}H_{18}O_2$ (MW 182.259): C, 72.49; H, 9.95. Found: C, 72.60; H, 10.16.

***rac*-(3a*R*,6*R*,6a*S*)-6-Hydroxyhexahydro-1(2*H*)-pentalenone (5a), *rac*-(3a*R*,6*S*,6a*S*)-6-Hydroxyhexahydro-1(2*H*)-pentalenone (5b), *rac*-(4*R*)-4-Hydroxybicyclo[3.2.1]octan-6-one, (6a), and *rac*-(4*S*)-4-Hydroxybicyclo[3.2.1]octan-6-one (6b).** Reagents: Mg (2.41 g, 99.1 mmol), 2-(2-bromoethyl)-1,3-dioxolane (8.95 g, 49.4 mmol), CuI (0.942 g, 4.95 mmol), **2a** (1.01 g, 12.3 mmol). Column chromatography (column A, *x*/*y*: 10/1, then 5/1) afforded **3a**[3] (0.972 g, 43%, pale-yellow oil). The yield was inferior under $CeCl_3$ catalysis.[6d] Hydrolysis of **3a** (972 mg, 5.3 mmol) followed by column chromatography (column A, *x*/*y*: 10/1, then 5/1) furnished **5a**[3] (391 mg, 53%, first fraction, whitish semisolid), **6b** (23 mg, 3%, second fraction, white solid), **5b** (64 mg, 9%, third fraction, whitish semisolid), **6a** (149 mg, 20%, fourth fraction, white solid). Compound **5a**: IR ν 3590, 3470, 1720, 1153, 1113, 1077 cm^{-1}; ^{1}H NMR δ 1.62−1.90 (m, 4H), 1.97

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(m, 1H), 2.14 (dddd, J = 13.0, 8.3, 8.3, 8.3 Hz, 1H), 2.22−2.46 (m, 2H), 2.70 (dd, J = 8.4, 8.4, Hz, 1H), 2.84 (m, 1H), 2.91 (br s, 1H, OH), 4.49 (ddd, J = 7.4, 4.5, 4.5 Hz, 1H); ^{13}C NMR δ 27.3, 30.6, 36.2, 39.9, 40.8, 56.9, 74.7, 222.1; MS (EI) *m*/*z* (% relative abundance) 140 (M^+, 8), 122 (26), 112 (7), 111 (14), 96 (61), 94 (13), 83 (100), 81 (47), 80 (73). Anal. Calcd for $C_8H_{12}O_2$ (MW 140.180): C, 68.54; H, 8.63. Found: C, 68.56; H, 8.79. Compound **5b**: IR ν 3600, 3410, 1716, 1146, 1040, 1022, 1006, 970 cm^{-1}; ^{1}H NMR δ 1.43 (m, 1H), 1.56−1.89 (m, 3H), 2.06−2.22 (m, 2H), 2.23−2.33 (m, 2H), 2.58 (d, J = 8.8 Hz, 1H), 3.01 (m, 1H), 3.19 (br s, 1H, OH), 4.33 (m, 1H); ^{13}C NMR δ 26.6, 30.9, 35.4, 38.0, 39.5, 61.9, 76.7, 220.9; MS (EI) *m*/*z* (% relative abundance) 140 (M^+, 57), 122 (64), 112 (69), 111 (60), 96 (84), 94 (52), 83 (96), 81 (72), 80 (79), 55 (100). Anal. Calcd for $C_8H_{12}O_2$ (MW 140.180): C, 68.54; H, 8.63. Found: C, 68.50; H, 8.78. Compound **6a**: mp 157−160 °C; IR ν 3560, 3445, 1732, 1160, 1070 cm^{-1}; ^{1}H NMR δ 1.36 (m, 1H), 1.63 (dd, J = 12.2, 3.2 Hz, 1H), 1.71 (m, 1H), 1.74 (m, 1H), 2.01−2.14 (m, 2H), 2.05 (dd, J = 18.5, 3.4, Hz, 1H), 2.27 (br s, 1H, OH), 2.26 (dd, J = 18.5, 6.8 Hz, 1H), 2.49 (m, 1H), 2.55 (m, 1H), 3.87 (m, 1H); ^{13}C NMR δ 29.1, 29.2, 31.5, 35.2, 43.8, 53.5, 71.9, 219.9; MS (EI) *m*/*z* (% relative abundance) 141 ($M^+ + 1$, 58), 140 (M^+, 62), 123 (72), 122 (74), 112 (27), 111 (41), 96 (81), 94 (63), 83 (97), 81 (89), 80 (100). Anal. Calcd for $C_8H_{12}O_2$ (MW 140.180): C, 68.54; H, 8.63. Found: C, 68.32; H, 8.67. Compound **6b**: mp 140−142 °C; IR ν 3605, 3430, 1730, 1156, 1012, 963 cm^{-1}; ^{1}H NMR δ 1.54 (m, 1H), 1.59−1.80 (m, 3H), 2.02 (dddd, J = 12.9, 12.9, 6.2, 2.3 Hz, 1H), 2.17 (dd, J = 18.5, 3.4 Hz, 1H), 2.29 (dd, J = 18.5, 6.5 Hz, 1H), 2.32 (ddd, J = 11.8, 3.4, 3.0 Hz, 1H), 2.37 (br s, 1H, OH), 2.50 (t, J = 4.9 Hz, 1H), 2.62 (m, 1H), 4.06 (m, 1H); ^{13}C NMR δ 26.5, 26.8, 30.0, 32.1, 42.6, 53.4, 67.5, 218.3; MS (EI) *m*/*z* (% relative abundance) 141 ($M^+ + 1$, 7), 140 (M^+, 13), 123 (9), 122 (4), 96 (59), 94 (11), 83 (100), 80 (30). Anal. Calcd for $C_8H_{12}O_2$ (MW 140.180): C, 68.54; H, 8.63. Found: C, 68.15; H, 8.67.

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Supporting Information Available: General experimental procedures; ^{13}C NMR for **3b**, **4b**, and **3a**; MS for **3b**; preparation and data for **4c**, **8**, **9**, *rac*-*N*′-[(3a*S*,6*R*,6a*R*)-6-hydroxyhexahydro-1(2*H*)-pentalenylidene]-4-methylbenzenesulfonohydrazide, **10**, **11**, **12a**,**b**, **13a**,**b**, and **14**−**17**; reduction of **14**; NMR Eu(fod)$_3$ data for **6a**,**b** and **13a**,**b** (Tables S1−S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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